Journal of the American College of Cardiology Vol. 47, No. 3 Suppl S

Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2004.11.075

Women and Ischemic Heart Disease

Pathophysiologic Implications From the Women's Ischemia Syndrome Evaluation (WISE) Study and Future Research Steps

Arshed A. Quyyumi, MD, FRCP

Atlanta, Georgia

The current review highlights gender-specific issues in ischemic heart disease (IHD) presentation, evaluation, and outcomes with a special focus on the results derived from the National Institutes of Health-National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation (WISE) study. New evidence on gender-based differences in vascular wall, atherosclerotic plaque deposition, pathophysiology, and innovative cardiovascular imaging techniques are reviewed. Critical areas of further inquiry needed to advance new gender-specific IHD understanding are detailed. (J Am Coll Cardiol 2006;47: 66S–71S) © 2006 by the American College of Cardiology Foundation

Recent observations pertaining to the diagnosis, prevalence, and progression of coronary artery disease (CAD) in women have increased the debate and controversy surrounding this condition that afflicts the vast majority of women living in the western hemisphere and is the predominant cause of their morbidity and mortality. It has been convincingly demonstrated that the incidence of CAD is lower in women than in men for all age groups except the very elderly. This has been offered as an explanation for the chronically reduced rate of diagnosis of underlying CAD in women either in its chronic stable state or in the setting of acute coronary syndromes (1). Yet it has also been shown, as recently reported from the Women's Ischemia Syndrome Evaluation (WISE) study database, that nearly 60% of women undergoing invasive evaluation for investigation of chest pain or abnormal noninvasive tests do not have any flow-limiting coronary stenoses at angiography. Thus, it appears that misdiagnosis of CAD and acute coronary events on the one hand, and an often inappropriate overuse of coronary angiography on the other, arises from the underappreciation by the medical community of the atypical symptomatic nature of presentation of CAD in women. The problem does not resolve, however, once the results of coronary angiography are available, as clearly demonstrated by the careful follow-up of such women in the WISE II study cohort. Even women found not to have significant coronary luminal narrowing suffered persistent or worsening symptoms, often demonstrated test abnormalities that implicated an ischemic etiology for their symptoms, were frequently chronically disabled, consumed tremendous health care resources, and, most importantly, experienced adverse cardiovascular events during medium-term follow up extending over a period of 4 to 5 years (2).

Thus, the challenges in understanding the manifestations of CAD in women include: 1) better understanding of the complexity of presenting symptoms that appear to be gender-specific; 2) defining appropriate noninvasive tests that should identify not only those with obstructive CAD but also the subset with normal coronary arteries who are at increased risk of cardiovascular event; and 3) understanding of the gender-specific pathophysiology of chest pain, ischemia, disability, and factors determining progression from minimal atherosclerosis to ischemic events. This task can only be accomplished by the discovery and adaptation of radically different approaches to diagnosis and management of cardiovascular diseases in women when appropriate. The standard approach of symptomatic presentation leading to stress testing, coronary angiography, and lesion-specific therapy, although reasonable in those with obstructive CAD, may not be appropriate for all women. Findings from the WISE studies have highlighted the pathophysiologic role of microvascular dysfunction, subendocardial ischemia, inflammation, genetic predisposition, and neurohormonal imbalance in imparting risk.

Myocardial ischemia and microvascular dysfunction. Although women undergoing coronary angiography present with chest pain suggestive of angina pectoris, it is clear that up to 50% of them will have normal or insignificant CAD, as compared to a 17% incidence in men (3). Yet a majority of these women also have abnormal stress tests that include either ST-segment depression during exercise, perfusion defects during radionuclide scintigraphy, or stress-induced wall motion abnormalities. This has given rise to the concept that these women have myocardial ischemia as a result of microvascular disease or dysfunction. However, the evidence for this in the vast majority of women presenting with chest pain has been missing and largely arises from stress tests that lack sufficient specificity (4). In fact studies have suggested that chest pain in many women is accompanied by a lowered pain threshold that may improve with imipramine therapy (5).

There is nevertheless evidence for myocardial ischemia in approximately 20% of women with chest pain and normal coronary arteries. Recent innovations in the application of phosphorus-31 nuclear magnetic resonance spectroscopy

From the Emory University School of Medicine, Atlanta, Georgia.
Manuscript received October 27, 2004; revised manuscript accepted November 18, 2004.

Abbreviations and Acronyms

CHD = coronary heart disease
CRP = C-reactive protein
DASI = Duke Activity Status Index
EPC = endothelial progenitor cell
IHD = ischemic heart disease
WISE = Women's Ischemia Syndrome Evaluation

have provided a means for monitoring changes in the myocardial high-energy phosphates, phosphocreatine, and adenosine triphosphate after stress. The WISE study investigators have shown a transient decrease in myocardial phosphocreatine/adenosine triphosphate ratio during handgrip exercise, indicating a shift toward anaerobic metabolism or myocardial ischemia in 20% of women with chest pain but no CAD (6). Subsequent three-year follow-up of 14 women with abnormal spectroscopy without CAD demonstrated an event rate similar to that observed in women with CAD and considerably worse than those with normal coronaries and normal spectroscopy (7).

The reasons for the development of ischemia with minimal exercise remain unknown. It is clear that focal epicardial spasm originally described by Prinzmetal et al. (8) accounts for <1% of ischemia in women undergoing angiography in the West. Vascular testing has revealed both microvascular smooth muscle dysfunction using adenosine or nitroprusside infusions and endothelial dysfunction using acetylcholine in 54% of the individuals (9), findings that appear to have prognostic value, as discussed in the following text. Thus, further investigations into the mechanisms underlying phosphocreatine uptake abnormalities despite lack of obstructive epicardial disease are warranted.

Risk factors and vascular disease. There is incontrovertible evidence to indicate that conventional risk factors for atherosclerosis account for the vast majority of the incident CAD observed in both men and women (10). However, it is also clear that knowledge of the presence or absence of these factors in an individual does not help precisely predict either the presence or extent of CAD, nor the future occurrence of adverse cardiovascular outcomes. This may be partly because the impact of risk factors in different individuals is variable and dependent on indeterminate factors such as duration of exposure and differing susceptibility. Understanding of the mechanisms underlying risk factor-mediated vascular injury has allowed us to develop tools to more accurately define risk in individual patients.

Oxidative stress. One proposed unifying mechanism explaining how disparate risk factors lead to CAD is oxidative stress, which occurs when the production of cellular oxidants exceeds the capacity of cellular antioxidant defense mechanisms (11). Virtually all of the known risk factors for atherosclerosis increase the production of reactive oxygen species in the vascular wall. Oxidative stress leads to endothelial dysfunction which in turn induces vascular inflammation that may promote further oxidative stress in a feed-forward fashion ultimately leading to atherosclerosis (12). Therefore, it is not surprising that markers of oxidative stress are proving to be early predictors not only of atherosclerotic vascular disease (13–16) but also of long-term prognosis (17,18). Serum and plasma myeloperoxidase (15,19), and isoprostane measurements appear to be important prognostic markers. Moreover, the redox state of common thiols, such as glutathione and cysteine, and measures of lipid peroxidation in the blood stream strongly and independently correlate with carotid intima-media thickening and endothelial dysfunction (20–22). Future studies evaluating risk of vascular disease in women should integrate these novel markers of oxidative stress.

Endothelial function. The term "endothelial function" refers to a multitude of physiologic functions of the vascular endothelium that maintain healthy homeostasis of the vascular wall, including normal vasomotion, inhibition of platelet aggregation and thrombus generation, and maintenance of relative impermeability. Cardiovascular risk factors activate a number of pro-oxidative processes that reduce the bioavailability of nitric oxide as part of the transition from normal endothelial function to endothelial dysfunction (23–25). Almost all conventional risk factors for atherosclerosis are associated with endothelial dysfunction. These include sedentary lifestyle and obesity, hypercholesterolemia, hyperhomocysteinemia, hypertension, diabetes, insulin resistance, smoking, and aging. Thus, the concept has been forwarded that endothelial vasodilator function is a reflection of the overall vascular health. Indeed, several studies in predominantly male populations demonstrated that endothelium-dependent vasomotor function of the coronary/brachial arteries predicted long-term cardiovascular risk, including acute cardiac and cerebrovascular events and development of hypertension (26–28).

The WISE study investigators studied coronary vascular endothelium-dependent and -independent function using intracoronary acetylcholine and nitroglycerin, respectively, in 163 women undergoing angiography. Almost 75% of the women had mild or no angiographic CAD, and during a four-year follow-up cardiovascular events were independently predicted by coronary vascular endothelial function independent of risk factors and extent of CAD (9). These data not only demonstrate that assessment of vascular endothelial function can provide an excellent prognostic tool in such women but also raise a couple of questions. First, does endothelial function predict outcome only in women with mild or no angiographic disease, or will this also apply to a larger group of women with and without risk factors or to those with extensive disease? Second, can endothelial function be considered a "target" for cardiovascular therapy where reversibility of dysfunction will be indicative of improvement in risk? This latter question was partly addressed in 400 postmenopausal women with hypertension (29). Event rates were seven-fold higher in those in whom brachial artery flow-mediated vasodilation did not improve by >10% compared with those who had improvement.

JACC Vol. 47, No. 3 Suppl S
February 7, 2006:66S–71S

Finally, techniques for assessment of coronary and peripheral endothelial function have been invasive, laborious, and technically challenging, impeding their widespread deployment. Newer and more reproducible techniques, including pulsatile arterial tonometry (30), which appears to correlate with risk factors and with coronary vascular endothelial function, need to be evaluated in future trials.

Inflammation. Elevated circulating levels of inflammatory markers have been associated with incident cardiovascular disease (31–33), linking chronic subclinical inflammation and atherosclerosis. In 14,719 apparently healthy women enrolled in the Women's Heath Initiative and followed for eight years, a higher high-sensitivity C-reactive protein (CRP) level imposed a higher risk of CAD events during follow-up even after correction for the components of the metabolic syndrome (34). The predictive value of inflammatory markers other than CRP has been investigated in the WISE study cohorts. In over 700 women undergoing angiography, serum amyloid A levels were highly and independently predictive of underlying CAD and of three-year outcomes, even after adjustment for CRP levels (35). When a larger panel of markers and a variable reduction approach was used to study a "proinflammatory" factor loaded on interleukin-6, CRP, and serum amyloid A, a "pro- and antiinflammatory" factor loaded on interleukin-18 and tumor necrosis factor-alpha, and an "immunosuppressive" factor loaded on transforming growth factor-beta, there was a significant increase in mortality with increases of the "proinflammatory" factor (hazard ratio is seven-fold greater in highest quartile compared to the lowest) (36). Such an approach seeking a panel of informative biomarkers that will be prognostic in women is desirable.

Obesity, insulin resistance, and metabolic syndrome. One factor that threatens to dramatically increase CAD prevalence is the impending epidemic of obesity (37,38) that affects all segments of the population, including women, children, and, most disturbingly, several minority ethnic populations (37,38). Although a large body of evidence supports the relationship between obesity and CAD mortality (39), the factors that mediate this increased risk are complex (40,41). The metabolic syndrome has recently been defined to capture the cluster of characteristics associated with obesity and high CAD risk: abdominal adiposity, high blood pressure, high blood glucose/insulin resistance, and an increased triglycerides/high-density lipoprotein ratio. Although the precise criteria remain controversial and the definition remains a work in progress, there is a consensus that these elements are important features of the syndrome (42–49). Strikingly, the National Health and Nutrition Examination Survey III data indicates that approximately 25% of the U.S. adult population 20 years or older and up to 45% of the population over 50 years or older meets the diagnostic criteria for the metabolic syndrome.

The WISE study has shed important light on the prevalence and impact of obesity, metabolic syndrome, and physical activity on cardiovascular risk in women admitted for angiography. In over 750 women studied, 34% were overweight, 42% were obese, and 58% had the metabolic syndrome. The presence of obesity did not predict either the underlying severity of CAD or event-free survival, whereas the presence of metabolic syndrome was associated with worse CAD severity, and a two-fold higher odds of suffering adverse CAD outcome during follow-up. This worse outcome was observed particularly in women with underlying CAD (50,51). Use of a self-reported index of physical activity (Duke Activity Status Index [DASI]) revealed that 70% of women had low functional capacity (DASI scores <25, equivalent to 7 metabolic equivalents). The occurrence of CAD and adverse events was correlated strongly with the DASI and not with obesity, with each metabolic equivalent increase in DASI associated with an 8% reduction in event rate (52).

The mechanisms underlying obesity and metabolic syndrome-related CAD risk have been studied in recent years. Not only is there an intimate association between obesity and insulin resistance (53,54), but also between obesity and the inflammatory markers fibrinogen and CRP (31,32,49,55–60). Waist circumference appears to correlate strongly with CRP and fibrinogen levels (61) and is stronger in women than in men (49), possibly owing to differing distribution of body fat compartments (visceral vs. subcutaneous) between the sexes (62–65). The adipose tissue is an active secretory organ that elaborates a variety of molecules known as adipocytokines, including tumor necrosis factor-alpha, interleukin-6, leptin, adiponectin, and resistin (66,67). Inflammatory marker and cytokine levels appear to predict future development of glucose intolerance (68,69) and vascular events (33,70). Subjects with the metabolic syndrome have higher levels of oxidized low-density lipoprotein, apolipoprotein B, urate, leukocytes, and erythrocyte sedimentation rate, lower apolipoprotein A concentrations, increased thrombotic tendencies, and reduced fibrinolytic tendencies (55,71). Insulin resistance is associated with quantitative and qualitative changes in lipoprotein particles and with endothelial activation (72,73). Other pathways up-regulated in the vasculature and adipose tissue include the endothelin system (74,75) and the renin-angiotensin cascade (76–79). Whether these measures of adipose tissue activation will be superior markers of cardiovascular risk over anatomic measures of obesity remains to be determined.

Ethnicity and genetics. The morbidity and mortality from atherosclerosis, particularly stroke, is considerably higher in African Americans compared to Caucasians (80–84), indicating potentially important genetic and environmental differences in organ function, socioeconomic status, and hemodynamic responses to environmental challenges between the races (85–87). Several intriguing ethnic and gender differences are evident in the prevalence of metabolic syndrome, insulin resistance, type 2 diabetes, and cardiovascular events. Black females have a larger waist and more hypertension and hyperglycemia but a lower frequency of

elevated triglyceride levels (37,38,88), leading to an underestimation of the prevalence of metabolic syndrome in black women. Insulin resistance is more common among black compared to white subjects for similar degree of adiposity (89,90), and African Americans have decreased insulin sensitivity and differences in insulin secretion and hepatic extraction of insulin compared with Caucasians.

Beyond racial differences, the importance of family history in development of CAD and its adverse events highlights the modulatory influence of the individual's genotype to vascular disease susceptibility. Several genetic polymorphisms associated with CAD or CAD events have been described in predominantly male populations. The WISE study has begun exploring the relationship between genotype and CAD incidence, and such efforts including larger numbers of ethnic minorities are going to be essential in understanding the influence of genetics on the vascular phenotype (91,92).

Vascular repair. The classic paradigm for inception of atherosclerosis states that endothelial cell injury is the stimulus for atherosclerotic plaque development (93) where seemingly disparate risk factors cause oxidative injury to the endothelium. Ultimately, the balance between injury and repair is thought to be the major determinant of cardiovascular disease progression, with endothelial progenitor cells (EPCs) playing an important role in vascular repair. Endothelial progenitor cell counts are lower in subjects with multiple risk factors, including diabetes and aging, and in those with endothelial dysfunction and CAD, indicating that increased oxidative stress may also lead to a depletion of dysfunction of the circulating EPC pool (94–98). Thus, EPCs may provide a circulating pool of cells that could constitute a cellular "repair" mechanism at the sites of vascular injury. Moreover, the observation that EPC activity can be stimulated with statin therapy raises the possibility that risk improvement may be partly mediated by restoration of EPC function (99–101).

Given that accelerated apoptosis of the injured endothelium and defective repair by an exhausted or senescent progenitor pool is the new paradigm that defines atherosclerotic disease prevalence and progression, it is timely to investigate how these concepts apply to women at risk. The EPC release is stimulated by the menstrual cycle in premenopausal women and it can be speculated that the lower susceptibility to atherosclerotic disease in this subset is at least partially explained by the increased availability of repair mechanisms. The observation that anemia is an important risk factor in women from the WISE study is also intriguing (102), and raises the question as to whether anemia is a manifestation of bone marrow hematopoietic progenitor cell pool defect that extends to endothelial progenitors and signifies reduced repair function. These aspects will need to be studied further.

Conclusions. The understanding of the pathophysiology of atherosclerotic disease and its progression in women has benefited from trials like the WISE study and others that have focused attention on the similarities and differences pertaining to gender. It has also allowed us to introduce new modalities to assess individual risk. Efforts to prospectively test these emerging concepts and strategies in larger populations need to continue.

Reprint requests and correspondence: Dr. Arshed A. Quyyumi, Emory University School of Medicine, 1364 Clifton Road NE, Suite D403C, Atlanta, Georgia 30322. E-mail: aquyyum@emory.edu.

REFERENCES

1. Pope JH, Aufderheide TP, Ruthazer R, et al. Missed diagnoses of acute cardiac ischemia in the emergency department. N Engl J Med 2000;342:1163–70.
2. Pepine CJ, Balaban RS, Bonow RO, et al. Women's Ischemic Syndrome Evaluation: current status and future research directions: Report of the National Heart, Lung, and Blood Institute Workshop: October 2–4, 2002: Section 1: Diagnosis of stable ischemia and ischemic heart disease. Circulation 2004;109:44e–6e.
3. Bairey Merz CN, Kelsey SF, Pepine CJ, et al. The Women's Ischemia Syndrome Evaluation (WISE) study: protocol design, methodology and feasibility report. J Am Coll Cardiol 1999;33:1453–61.
4. Panza M, Julio A, Laurienzo R, et al. Investigation of the mechanism of chest pain in patients with angiographically normal coronary arteries using transesophageal dobutamine stress echocardiography. J Am Coll Cardiol 1997;29:293–301.
5. Cannon RO, Quyyumi AA, Mincemoyer R, et al. Imipramine in patients with chest pain despite normal coronary angiograms. N Engl J Med 1994;330:1411–7.
6. Buchthal SD, den Hollander JA, Bairey Merz CN, et al. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. N Engl J Med 2000;342:829–35.
7. Johnson BD, Shaw LJ, Buchthal SD, et al. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute–sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 2004;109:2993–9.
8. Prinzmetal M, Kennamer R, Merliss R, et al. Angina pectoris. I. A variant form of angina pectoris; preliminary report. Am J Med 1959;27:375–88.
9. von Mering GO, Arant CB, Wessel TR, et al. Abnormal coronary vasomotion as a prognostic indicator of cardiovascular events in women: results from the National Heart, Lung, and Blood Institute-sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 2004;109:722–5.
10. Yusuf S, Ounpuu S, Dans T, INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–52.
11. McCord JM. The evolution of free radicals and oxidative stress. Am J Med 2000;108:652–9.
12. Fukui T, Ishizaka N, Rajagopalan S, et al. p22phox mRNA expression and NADPH oxidase activity are increased in aortas from hypertensive rats. Circ Res 1997;80:45–51.
13. Hulthe J, Bokemark L, Fagerberg B. Antibodies to oxidized LDL in relation to intima-media thickness in carotid and femoral arteries in 58-year-old subjectively clinically healthy men. Arterioscler Thromb Vasc Biol 2001;21:101–7.
14. Puurunen M, Manttari M, Manninen V, et al. Antibody against oxidized low-density lipoprotein predicting myocardial infarction. Arch Intern Med 1994;154:2605–2609.
15. Zhang R, Brennan ML, Fu X, et al. Association between myeloperoxidase levels and risk of coronary artery disease. JAMA 2001;286:2136–42.
16. Shishehbor MH, Aviles RJ, Brennan M-L, et al. Association of nitrotyrosine levels with cardiovascular disease and modulation by statin therapy. JAMA 2003;289:1675–80.

17. Brennan M-L, Penn MS, Van Lente F, et al. Prognostic value of myeloperoxidase in patients with chest pain. N Engl J Med 2003; 349:1595–604.
18. Blankenberg S, Rupprecht HJ, Bickel C, et al. Glutathione peroxidase 1 activity and cardiovascular events in patients with coronary artery disease. N Engl J Med 2003;349:1605–13.
19. Brennan M, Penn M, Van Lente F, et al. Prognostic value of myeloperoxidase in patients with chest pain. N Engl J Med 2003; 349:1595–604.
20. Jones DP, Carlson JL, Mody VC Jr., Cai J, Lynn MJ, Sternberg P Jr. Redox state of glutathione in human plasma. Free Radical Biol Med 2000;28:625–35.
21. Jones D. Redox potential of GSH/GSSG couple: assay and biological significance. Methods Enzymol 2002;348:93–112.
22. Ashfaq S, Beinart SC, Abramson JL, et al. Plasma glutathione redox state: a novel marker of oxidative stress, correlates with early atherosclerosis in humans. J Am Coll Cardiol 2003;41 Suppl A:293A–4A.
23. Quyyumi AA. Endothelial function in health and disease: new insights into the genesis of cardiovascular disease. Am J Med 1998;105:32S–9S.
24. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res 2000;87:840–4.
25. Dzau VJ. Tissue angiotensin and pathobiology of vascular disease: a unifying hypothesis. Hypertension 2001;37:1047–52.
26. Bonetti PO, Lerman LO, Lerman A. Endothelial dysfunction: a marker of atherosclerotic risk. Arterioscler Thromb Vasc Biol 2003; 23:168–75.
27. Verma S, Buchanan MR, Anderson TJ. Endothelial function testing as a biomarker of vascular disease. Circulation 2003;108:2054–9.
28. Halcox JPJ, Schenke WH, Zalos G, et al. Prognostic value of coronary vascular endothelial dysfunction. Circulation 2002;106: 653–8.
29. Modena MG, Bonetti L, Coppi F, Bursi F, Rossi R. Prognostic role of reversible endothelial dysfunction in hypertensive postmenopausal women. J Am Coll Cardiol 2002;40:505–10.
30. Kuvin JT, Patel AR, Sliney KA, et al. Assessment of peripheral vascular endothelial function with finger arterial pulse wave amplitude. Am Heart J 2003;146:168–74.
31. Haverkate F, Thompson SG, Pyke SDM, Gallimore JR, Pepys MB, Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group E. Production of C-reactive protein and risk of coronary events in stable and unstable angina. Lancet 1997;349: 462–6.
32. Koenig W, Sund M, Frohlich M, et al. C-reactive protein, a sensitive marker of inflammation, predicts future risk of coronary heart disease in initially healthy middle-aged men: results from the MONICA (Monitoring Trends and Determinants in Cardiovascular Disease) Augsburg cohort study, 1984 to 1992. Circulation 1999;99:237–42.
33. Ridker PM, Cushman M, Stampfer M, Tracy R, Hennekens CH. Inflammation, aspirin and the risk of cardiovascular disease in apparently healthy men. N Engl J Med 1997;336:973–9.
34. Ridker PM, Buring JE, Cook NR, Rifai N. C-reactive protein, the metabolic syndrome, and risk of incident cardiovascular events: an 8-year follow-up of 14,719 initially healthy American women. Circulation 2003;107:391–7.
35. Johnson BD, Kip KE, Marroquin OC, et al. Serum amyloid A as a predictor of coronary artery disease and cardiovascular outcome in women: the National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 2004; 109:726–32.
36. Kip KE, Marroquin OC, Shaw LJ, et al. Global inflammation predicts cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. Am Heart J 2005; 150:900–6.
37. Flegal KM, Carroll MD, Ogden CL, Johnson CL. Prevalence and trends in obesity among U.S. adults, 1999–2000 (comment). JAMA 2002;288:1723–7.
38. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among U.S. children and adolescents, 1999–2000 (comment). JAMA 2002;288:1728–32.
39. Sowers JR. Obesity as a cardiovascular risk factor. Am J Med 2003;115:37S–41S.
40. Hajjar I, Kotchen TA. Trends in prevalence, awareness, treatment, and control of hypertension in the United States, 1988–2000 (comment). JAMA 2003;290:199–206.
41. Din-Dzietham R, Nembhard W, Collins R, Davis SK. Race-based discrimination at work is associated with hypertension in African-Americans. The Metro Atlanta Heart Study. Social Sci Med 2004; 58:449–61.
42. Reaven G. Banting lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595–607.
43. Modan M, Almog S, Lusky A, Eshkol A, Shefi M, Shitrit A, Fuchs Z. Hyperinsulinemia. A link between hypertension obesity and glucose intolerance. J Clin Invest 1985;75:809–17.
44. Ferrannini E, Bonadonna R, Giorico MA, et al. Insulin resistance in essential hypertension. N Engl J Med 1987;317:350–7.
45. Kaplan N. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. Arch Intern Med 1989;149:1514–20.
46. Bjorntorp P. Metabolic implications of body fat distribution. Diabetes Care 1991;14:1132–43.
47. Boyko EJ, Bergstrom RW, Newell-Morris L, Fujimoto WY. Visceral adiposity, fasting plasma insulin, and blood pressure in Japanese-Americans. Diabetes Care 1995;18:174–81.
48. Frayn KN. Insulin resistance, adipose tissue and coronary heart disease. Clin Sci (Lond) 1992;82:1–8.
49. Ford ES, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. JAMA 2002;287:356–9.
50. Kip KE, Marroquin OC, Kelley DE, et al. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women: a report from the Women's Ischemia Syndrome Evaluation (WISE) study. Circulation 2004;109:706–13.
51. Marroquin OC, Kip KE, Kelley DE, et al. Metabolic syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women: a report from the Women's Ischemia Syndrome Evaluation. Circulation 2004;109:714–21.
52. Wessel TR, Arant CB, Olson MB, et al. Relationship of physical fitness vs body mass index with coronary artery disease and cardiovascular events in women. JAMA 2004;292:1179–87.
53. Karter AJ, Selby JV, D'Agostino RB Jr., et al. Insulin sensitivity and abdominal obesity in African-American, Hispanic, and non-Hispanic white men and women. The Insulin Resistance and Atherosclerosis Study. Diabetes 1996;45:1547–55.
54. DeFronzo RA. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991;14:173–94.
55. Juhan-Vague I. PAI-1, obesity, insulin resistance and risk of cardiovascular events. Thromb Haemost 1997;78:656–60.
56. Maresca G, Di Blasio A, Marchioli R, Di Minno G. Measuring plasma fibrinogen to predict stroke and myocardial infarction: an update. Arterioscler Thromb Vasc Biol 1999;19:1368–77.
57. Yudkin JS, Stehouwer CDA, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999;19:972–8.
58. Festa A, D'Agostino R Jr., Mykkanen L, et al. Relative contribution of insulin and its precursors to fibrinogen and PAI-1 in a large population with different states of glucose tolerance: the Insulin Resistance Atherosclerosis Study (IRAS). Arterioscler Thromb Vasc Biol 1999;19:562–8.
59. Jazet IM, Pijl H, Meinders AE. Adipose tissue as an endocrine organ: impact on insulin resistance. Netherlands J Med 2003;61:194–212.
60. Kadowaki T, Hara K, Yamauchi T, Terauchi Y, Tobe K, Nagai R. Molecular mechanism of insulin resistance and obesity. Exp Biol Med 2003;228:1111–7.
61. Hak AE, Stehouwer CDA, Bots ML, et al. Associations of C-reactive protein with measures of obesity, insulin resistance, and subclinical atherosclerosis in healthy, middle-aged women. Arterioscler Thromb Vasc Biol 1999;19:1986–91.
62. Seidell JC, Thijssen MA, Burema J, Deurenberg P, Hautvast JG, Ruijs JH. Assessment of intra-abdominal and subcutaneous abdominal fat: relation between anthropometry and computed tomography. Am J Clin Nutr 1987;45:7–13.

63. Pouliot MC, Lemieux S, Moorjani S, Bouchard C, Tremblay A, Nadeau A, Lupien PJ. Waist circumference and abdominal sagittal diameter: best simple anthropometric indexes of abdominal visceral adipose tissue accumulation and related cardiovascular risk in men and women. Am J Cardiol 1994;73:460–8.
64. Duncan BB, Chambless LE, Schmidt MI, et al. Correlates of body fat distribution: variation across categories of race, sex, and body mass in the Atherosclerosis Risk in Communities study. Ann Epidemiol 1995;5:192–200.
65. Kvist H, Grangard U, Tylen U, Sjostrom L. Total and visceral adipose-tissue volumes derived from measurements with computed tomography in adult men and women: predictive equations. Am J Clin Nutr 1988;48:1351–61.
66. Hotamisligil GS AP, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995;95:2409–15.
67. Steppan CM, Lazar MA. Resistin and obesity-associated insulin resistance. Trends Endocrinol Metab 2002;13:18–23.
68. Pradhan AD MJ, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. JAMA 2001;286:327–34.
69. Schmidt MI, Duncan BB, Sharrett AR, et al. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. Lancet 1999;353:1649–52.
70. Thompson SG, Kienast J, Pyke SDM, Haverkate F, van de Loo JCW, European Concerted Action on Thrombosis and Disabilities Angina Pectoris Study Group. Hemostatic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. N Engl J Med 1995;332:635–41.
71. Juhan-Vague I, Pyke SDM, Alessi MC, Jespersen J, Haverkate F, Thompson SG. Fibrinolytic factors and the risk of myocardial infarction or sudden death in patients with angina pectoris. Circulation 1996;94:2057–63.
72. Tan E-S, van der Meer J, de Kam PJ, et al. Worse clinical outcome but similar graft patency in women versus men one year after coronary artery bypass graft surgery owing to an excess of exposed risk factors in women (for CABADAS:Research Group of the Interuniversity Cardiology Institute of the Netherlands). J Am Coll Cardiol 1999;34:1760–8.
73. Vakkilainen J, Makimattila S, Seppala-Lindroos A, et al. Endothelial dysfunction in men with small LDL particles. Circulation 2000;102:716–21.
74. Piatti PM, Galli L, Fragasso G, Valsecchi G, Conti M, Gernone F, Pontiroli AE. Relationship between endothelin-1 concentration and metabolic alterations typical of the insulin resistance syndrome. Metabolism 2000;49:748–52.
75. Irving RJ, Noon JP, Watt GCM, Webb DJ, Walker BR. Activation of the endothelin system in insulin resistance. QJM 2001;94:321–6.
76. Lind L RR, Andersson PE, Haenni A, Lithell H. Insulin resistance in essential hypertension is related to plasma renin activity. J Hum Hypertens 1998;12:379–82.
77. Weiss D, Sorescu D, Taylor WR. Angiotensin II and atherosclerosis. Am J Cardiol 2001;87:25–32.
78. Engeli S, Feldpausch M, Gorzelniak K, et al. Association between adiponectin and mediators of inflammation in obese women. Diabetes 2003;52:942–7.
79. Ching SF HL, Slakey LL. Angiotensin converting enzyme in cultured endothelial cells and growth medium. Relationships to enzyme from kidney and plasma. Biochim Biophys Acta 1981;657:222–31.
80. U.S. Census. Statistical Abstract of the United States. Springfield, VA: National Technical Information Service (NTIS), 1997.
81. Gillum RF, Mussolino ME, Madans JH. Coronary heart disease incidence and survival in African-American women and men: the NHANES I epidemiologic follow-up study. Ann Intern Med 1997;127:111–8.
82. Sempos C CR, Kovar MG, McMillen M. Divergence of the recent trends in coronary mortality for the four major race-sex groups in the United States. Am J Public Health 1988;78:1422–7.
83. American Heart Association. Heart Disease and Stroke Statistics—2003 Update. Dallas, TX: American Heart Association, 2002.
84. Ninomiya JK, l'Italien G, Criqui MH, Whyte JL, Gamst A, Chen RS. Association of the metabolic syndrome with history of myocardial infarction and stroke in the third National Health and Nutrition Examination Survey. Circulation 2004;109:42–6.
85. Gillum R. Pathophysiology of hypertension in blacks and whites. A review of the basis of racial blood pressure differences. Hypertension 1979;1:468–75.
86. Falkner B. Differences in blacks and whites with essential hypertension: biochemistry and endocrine. State of the art lecture. Hypertension 1990;15:681–6.
87. Anderson NB, Pickering T, Jackson JS. Hypertension in blacks: psychosocial and biological perspectives. J Hypertens 1989;7:161–72.
88. Park YW, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the U.S. population from the third National Health and Nutrition Examination Survey, 1988–1994 (comment). Arch Intern Med 2003;163:427–36.
89. Carnethon MR, Palaniappan LP, Burchfiel CM, Brancati FL, Fortmann SP. Serum insulin, obesity, and the incidence of type 2 diabetes in black and white adults: the Atherosclerosis Risk in Communities study: 1987–1998 Diabetes Care 2002;25:1358–64.
90. Palaniappan LP, Carnethon MR, Fortmann SP. Heterogeneity in the relationship between ethnicity, BMI, and fasting insulin. Diabetes Care 2002;25:1351–7.
91. Chen Q, Reis SE, Kammerer CM, et al. APOE polymorphism and angiographic coronary artery disease severity in the Women's Ischemia Syndrome Evaluation (WISE) study. Atherosclerosis 2003;169:159–67.
92. Chen Q, Reis SE, Kammerer C, et al. Genetic variation in lectin-like oxidized low-density lipoprotein receptor 1 (LOX1) gene and the risk of coronary artery disease. Circulation 2003;107:3146–51.
93. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993;362:801–9.
94. Vasa M, Fichtlscherer S, Aicher A, et al. Number and migratory activity of circulating endothelial progenitor cells inversely correlate with risk factors for coronary artery disease. Circ Res 2001;89:E1–7.
95. Hill JM, Zalos G, Halcox JP, et al. Circulating endothelial progenitor cells, vascular function, and cardiovascular risk. N Engl J Med 2003;348:593–600.
96. Tepper OM, Galiano RD, Capla JM, et al. Human endothelial progenitor cells from type II diabetics exhibit impaired proliferation, adhesion, and incorporation into vascular structures. Circulation 2002;106:2781–6.
97. H Geiger GVZ. The aging of lympho-hematopoietic stem cells. Nat Immunol 2002;3:329–33.
98. Rauscher FM, Goldschmidt-Clermont PJ, Davis BH, et al. Aging, progenitor cell exhaustion, and atherosclerosis. Circulation 2003;108:457–63.
99. Dimmeler S, Aicher A, Vasa M, et al. hMG-CoA reductase inhibitors (statins) increase endothelial progenitor cells via the PI 3-kinase/Akt pathway. J Clin Invest 2001;108:391–7.
100. Llevadot J, Murasawa S, Kureishi Y, et al. hMG-CoA reductase inhibitor mobilizes bone marrow-derived endothelial progenitor cells. J Clin Invest 2001;108:399–405.
101. Vasa M, Fichtlscherer S, Adler K, et al. Increase in circulating endothelial progenitor cells by statin therapy in patients with stable coronary artery disease. Circulation 2001;103:2885–90.
102. Arant CB, Wessel TR, Olson MB, et al. Hemoglobin level is an independent predictor for adverse cardiovascular outcomes in women undergoing evaluation for chest pain: results from the National Heart, Lung, and Blood Institute Women's Ischemia Syndrome Evaluation study. J Am Coll Cardiol 2004;43:2009–14.